Association between Fish Consumption and Risk of Dementia: A New Study from China and A Systematic Literature Review and Meta-Analysis

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Abstract

Objective: To assess the association of fish consumption with the risk of dementia and its dose-response relationship, and investigate variations in the association among low, middle and high-income countries.

*Design***:** A new community-based cross-sectional study and a systematic literature review
*Settings***:** Urban and rural communities in China; population-based studies systematically searched from worldwide literature.
*Subjects***:** 6981 Chinese aged ≥ 60 years in six provinces took part in a household health survey of dementia prevalence and risk factors in China. In addition, 33964 participants from 11 published and eligible studies were included in the systematic review and meta-analysis.
Results: In the new study in China, 326 participants were diagnosed with dementia (4.7%); those that consumed any amount of fish in the past 2 years compared to those who consumed no fish had reduced risk of dementia (adjusted odds ratio 0.73, 95% CI 0.64-0.99), but the dose-response relationship was not statistically significant. The meta-analysis from available data from the literature and the new study showed a relative risk (RR) of dementia of 0.80 (95%CI 0.74-0.87) for people with fish consumption, and the impact was similar among countries with different levels of income. Pooled dose-response data revealed a RR of 0.84 (0.72-0.98), 0.78 (0.68-0.90) and 0.77 (0.61-0.98) in people with low, middle and high consumption of fish respectively. The matched figures for Alzheimer's disease (AD) were 0.88 (0.74-1.04), 0.79 (0.65-0.96) and 0.67 (0.58-0.78) respectively.

Conclusions: Greater consumption of fish is associated with a lower risk of dementia. Increasing fish consumption may help prevent dementia worldwide regardless of income levels.

Keywords: Dementia, Alzheimer's disease, Fish consumption

Introduction

Dementia is a major global public health challenge. There are 46.8 million people living with dementia in the world, a number that is predicted to rise to 131.5 million by 2050[1]. There is no known cure for dementia, and thus more efforts have been made to investigate its risk or protective factors for prevention. Previous studies showed that eating fish was related to reduced risks of cardiovascular diseases (e.g. coronary heart disease[2], stroke[3]), respiratory disease[4] and depression[5]. There are also some studies suggesting that fish consumption could improve cognitive function across the life course[6], mainly in young people[7].

Since fish fatty acids are important constituents for proper brain functioning and neurocognitive development[8], there has been an increase in research investigating whether fish consumption could reduce the risk of dementia[9]. However, the findings from those studies are not consistent[10, 11]. Some studies suggested that fish consumption was associated with a reduced risk of dementia[12, 13], while others did not show such an association[14, 15]. Previous studies on fish consumption and dementia are predominately from high income countries, where the characteristics of population would make difficulties in dealing with confounding effects including high levels of cardiovascular diseases and risk factors on the association between fish consumption and dementia risk and the findings could not be generalised to other countries. There is lack of data[16] from low- and middle-income countries (LMIC), where people have high risk of dementia but low level of fish consumption[1]. Although there were meta-analyses published previously[16-18] to investigate the association of fish consumption with risk of dementia, inferences from those meta-analysis studies were hindered by several potential limitations, for instance, missing relevant key publications[9]. In this paper, we examined data from a large-scale household health survey in China and carried out an updated systematic worldwide literature review and meta-analysis to investigate the association of fish consumption with risk of dementia and its dose-response relationship, and to examine any differences in the association between high income countries and LMICs.

Methods

A multi-province health survey study of older people in China

We analysed data from the multi-province health survey study of dementia in China. The methods of the studied populations and interview outcomes have been fully reported before[19, 20]. In brief, during 2007-2010, we carried out a large-scale health survey study of older people in the provinces of Guangdong, Heilongjiang, Shanghai and Shanxi, Anhui and Hubei in China to investigate prevalence, risk factors and care of dementia and other chronic conditions[20, 21].

The Four-Province Study: In 2008-2009 we selected one rural and one urban community from each of the four provinces (Guangdong, Heilongjiang, Shanghai, Shanxi) as the study fields. We tried to recruit no fewer than 500 participants in each community and employed a cluster randomised sampling method to choose residential communities (the district in urban areas and the village in rural) from each of the four provinces. The target population consisted of residents aged ≥60 years living in the area for at least 5 years. Based on the residency list of the committees of the village and the district, we recruited a total of 4314 participants with an overall response rate of 93.8%. The local survey team interviewed the participants at home. The main interview included a general health and risk factors record, the Geriatric Mental State (GMS) questionnaire[22] and other components of the 10/66 algorithm dementia research package[23]. We carried out a two-phase interview to save our research resources. In phase one, we completed the general health and risk factors record, the GMS, the Community Screening Instrument for Dementia (CSI-D) cognitive test and Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Using three of the four constituent components of the 10/66 algorithm (i.e. data of GMS-AGECAT, the CSI-D cognitive test and CERAD interview), we calculated a probability of possible dementia for each participant. In phase two, we selected the top 15% of the population who had the highest probability of having "dementia" as "probable cases" and a random sample of 5% of the rest as "probable non-cases" for subsequent interviews in each province. The interview team completed the CSI-D informant interview for the selected participants.

The Anhui study: Using the same interview approach as those in the 4-province study, we completed interviews of 1757 older people from the 3rd wave survey of the Anhui cohort[20], the initial number of which was 3336 participants at baseline aged ≥60 years who were randomly recruited in 2001 and 2003 respectively.

The Hubei study: In 2010-2011 we extended the project to include the Hubei province[20]. We used the same protocol and interview materials as the Four-province study but interviewed all participants at one stage phase using the full 10/66 methods. We recruited 1,001 participants aged ≥ 60 years and achieved a response rate of 91.8%.

Risk factors*:* In the general health and risk factors questionnaire interview, we recorded details relating to socio-demography, lifestyle, social networks and support, histories of chronic diseases and risk factors[24]. We measured height, weight, waist circumference and blood pressure for all participants. In the interview, we asked each participant for details of dietary intakes, including rice, wheat flour, meat, fish, egg, fresh vegetable, fruit, chilli pepper, garlic, ginger and different types of vegetable oils. All participants were required to provide the answer to the frequency of fish consumption in the past two years: (1) *Never eat*, (2) ≤*Once a week*, (3) >*Once a week and < Daily*, (4) *Once a day*, and (5) ≥ *Twice a day*.

Diagnosis of dementia: The GMS data were analysed by a computer program-assisted diagnosis, the Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT), to assess the principal mental disorders in the study participants[22]. We employed the 10/66 dementia algorithm to diagnose dementia, which included the data from the GMS-AGECAT diagnostic output, the CSI-D, COGSCORE, the CSI-D informant interview (RELSCORE), and the CERAD ten-word list learning task with delayed recall[23, 25]. We used a cut-off point of probability (≥0.25) derived from the full 10/66 algorithm to diagnose dementia, which has been validated in China[26]. Three hundred and twenty-six participants were diagnosed to have dementia.

Data Analysis

We employed a binary logistic regression model to calculate Odd Ratios (ORs) and their 95% Confidence Intervals (CIs) of dementia in participants with different levels of fish consumption in comparison to those with no fish consumption over the past 2 years. In the model, we adjusted for age, sex, province, urban-rural areas, education level, smoking status and stroke. The data analysis was conducted using SPSS (version 20).

Systematic literature review

Four authors (A.B., R.C, I.D., and W.Z.) independently searched and re-searched literature from databases of Medline, PubMed, CINAHL, Psych-info and Psychology and Behavioural Sciences Collection. The strategy for the database search was developed using the Population, Exposure and Outcome framework (PEO)[27]. The search terms were ["dementia" OR "Alzheimer's disease"] AND ["fish"]. The literature was searched from the earliest dates of each of the databases to 30th November 2016. The search for relevant articles included all studies with no language restriction. We read the title and abstract of the searched studies. The studies selected were appropriate for this review if they investigated an association between fish consumption and dementia (or Alzheimer's disease (AD)) in the population. Alongside the electronic database search explored, a manual reference search was also conducted to find additional articles missed by the online search. If two articles were published from the same cohort data but in different follow-up durations[28, 29], we would use the longest follow-up study paper for review.[29] Figure 1 shows the study selection process. We identified 11 original studies eligible for review. Following the PRISMA[27] guidelines, we (A.B., I.D., W.Z., and G.Q.) conducted a systematic review. Each of the articles was reviewed by two reviewers and assessed independently using a predesigned data extraction form to extract the necessary information from the chosen studies. Differences in reviewing literature and extracting data between the two reviewers would be resolved through face-to-face discussion, and if the differences remained the 3rd reviewer would have the discussion with them to make the agreement. The quality assessment of the articles was achieved by employing the Newcastle-Ottawa Scale[30] and the AXIS tool[31].

Meta-analysis

Data (Odds ratios (ORs), Rate ratios or Hazard ratios (HRs) and their 95% CIs) were pooled from published studies and the new study. All these measures and their 95% CIs were pooled together as a relative risk (RR) with the assumption of achieving a common unit of comparison. We analysed the data grouped by studied population in each of the study which we selected to investigate all types of dementia in relation to fish consumption. The studied population was defined as each individual sample in the study according to its place (country, regions, etc), time (years) and person (ethnicity, etc) where applicable. A random effect model was employed if the heterogeneity of the within and between studies variation were significant; otherwise a fixed effect model was used. Publication bias was evaluated using the Egger's regression[32]. First, we tried to assess an overall RR of dementia in participants who consumed fish in comparison with those who did not. If the article only gave the RRs in different levels of fish consumption, we took the figure from the highest fish consumption group for analysis. If the article only gave the figures from the continuous data analysis of fish consumption or from only high vs low levels of fish consumption, we took them in the meta-analysis. Second, we stratified the identified studies for meta-analysis according to the number of the groups of fish consumption measured at differing levels. This would help to examine differences in the RR among studies with different levels of fish consumption data analysis. Third, we investigated a dose-response association between fish consumption and risk of dementia according to low, middle and high consumption versus no/rare consumption. Where an article only gave the figure from the continuous data analysis of fish consumption or from only two groups of fish consumption (high vs low level) we took it in the middle level of fish consumption for the meta-analysis. If the article only provided the data of RR and 95%CIs from the middle and high levels of fish consumption versus no/rare consumption, we took them in the middle and high group levels for pooling the data. We examined any differences in the impact of fish consumption on the risk of dementia among LMICs and high-income countries. We also investigated any influence of the study design (cases-control studies, cross-sectional studies, and cohort studies) and duration of the cohort follow up on the association. We repeated above analyses for AD, where the data were available. All analyses were performed in STATA (version 14.2 software StataCorp).

Results

The six provinces study of China

Of 7072 participants, 6981 (98.7%) provided information on fish consumption. Their average age was 62.6±12.2 years, and 54.0% were women. In total, 1528 participants (21.9%) did not eat fish over the past 2 years, 2631 (37.7%) consumed fish once a week, 1938 (27.8%) ≥twice a week and 884 (12.7%) ≥ once a day. We examined the demographic characteristics of participants in each of these four groups (data not shown). Table 1 shows numbers, percentages and ORs of dementia in participants with different levels of fish consumption. The risk of dementia decreased with increased consumption of fish, although participants who consumed fish ≥once a day had the highest prevalence of dementia. After adjusting for age, sex, stroke and other confounding factors, we found that participants with different levels of fish consumption had a reduced risk of dementia (the details of ORs seen in Table 1), but there seemed no significant "dose response" relationship. Participants with any level of fish consumption had a 27% significant reduction in the risk of dementia (adjusted OR 0.73, 95% 0.64-0.99) in comparison with those who did not consume fish over the past two years.

Systematic literature review

In the 11 identified articles, we found that all were from high income countries, except for one study led by the UK [33] which included 7 studied populations from LMICs. They were published between 2002 and 2011. One of the studies was cross-sectional[33], 3 were case-control[34-36] and 7 were cohort[9, 12, 13, 29, 37-39]. These articles included 17 studied populations (one study[33] covered 7 populations). Their sample size varied from 57 to 14956, with a total of 33964 participants, and the minimum age in these studies' populations varied from 55 to 76 years. A food frequency questionnaire (FFQ) was used in four of the studies [12, 13, 37, 38], a semi quantitative food frequency questionnaire (SFFQ) was used in another three[9, 36, 39]. A meal-based check list alongside SFFQ was used in one [29], and the remaining one used a face-to-face standard method of assessment to evaluate the participant's fish intake[33]**.** Four of the studied populations reported a statistically significant association of fish consumption with reduced risk of dementia, although two of them[34, 35] did not present the effect sizes. Data from 11 studied populations reported an association but a non-statistically significant reduction, while two exhibited no association (or increased risk) [29, 33]. Online Tables 1 and 2 document the details of the studies' characteristics and outcomes. We examined the quality of each of these studies and found that the quality of these articles was in general good (online Table 3).

Meta-analysis

After excluding two studies that did not present the effect sizes,[34, 35] we took data from 15 studied populations reported within 9 published studies, and the data from the 6-provinces study of China for the meta-analysis. Figure 2 shows a forest plot of the findings of the association between fish consumption and dementia risk. In total, 3139 dementia cases in 40,668 participants were analysed. Data from these studied populations suggested little variability in the associated effects between studies with only one study showing an increased risk (albeit not statistically significant) of dementia with higher fish consumption. The fixed effect model analysis showed that there was a 20% reduction in the risk of dementia in participants who consumed fish (or consumed fish at a higher level) compared to those who did not eat fish (or who consumed fish at a lower level). There was little evidence of publication bias; the Egger method of bias estimate showed a p-value of 0.597 (online Figure 1).

Data from different study designs or from different level measures of fish consumption showed no significant differences in RR for dementia risk in relation to fish consumption (Table 2). The association of fish consumption with dementia risk was similar between high income countries (RR 0.83, 0.71- 0.97) and LMICs (RR 0.79, 0.72 -0.88) (Table 2).

Of 16 studied populations from nine articles [including the new study in China] for the meta-analysis, two[(33)] [(37)] showed a significant trend for a dose-response relationship. The pooled data showed a reduced RR of 0.84 (0.72, 0.98) in dementia in participants with a low level of fish consumption, of 0.78 (0.68, 0.90) in a middle level of fish consumption, and of 0.77 (0.61, 0.98) in a high level of fish consumption (Table 3).

AD data analysis In all 7 studied populations which examined the risk of AD specifically in relation to fish consumption[(9, 12, 13, 29, 37-39)], the pooled data (in total 1105 cases of AD) showed a significant impact of fish consumption on reduced risk of AD (RR 0.73, 95% CI 0.65-0.82) (the forest plot shown in Figure 3). All studies were undertaken in high income countries, and of cohort design. The patterns for the impact of fish consumption on reduced risk of AD (Online Table 4) were similar to those in all dementia, and it may have a stronger dose-response relationship in comparison with those in dementia (see Table 3).

Discussion

Our study examined the data from a large-scale health survey of dementia prevalence and risk factors in China and completed a systematic literature review and meta-analysis to assess the association of fish consumption with dementia and AD risks in countries of different levels of income. We have found that increased consumption of fish was significantly associated with a reduced risk of dementia, and there was a stronger dose-response relationship between fish consumption and a reduced risk of AD.

The observed inverse association between the risk of dementia and fish consumption is biologically plausible. Fish is the major dietary source of omega-3 polyunsaturated fatty acids (PUFAs), which comprise of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), being collectively called the fish fatty acids[40, 41]. Previous studies have suggested the preventative effect of fish consumption and its constituent (omega-3 fatty acid) on cardiovascular disease, through inflammation reduction, blood pressure reduction and endothelial function enhancement[3]. Fish consumption has been shown to have a preventative effect on reducing the risks of coronary heart disease (RR 0.62, 95% CI 0.46-0.82)[2] and stroke (RR 0.94, 95% CI 0.89–0.99)[3]. These are co-morbidities associated with dementia [42]. Therefore, reducing these diseases may be one of the pathways for the preventative impact of fish consumption on dementia.

Strengths and Limitations of the study

The main strength of this paper is the inclusion of both original data from a large-scale health survey from China and data from all other relevant studies worldwide based on a systematic search and review. Older Chinese citizens have higher levels of socioeconomic deprivation, but low levels of cardiovascular risk factors (e.g. obesity) and depression[24]. These special population characteristics of older Chinese residents helped to assess the association of fish consumption with the risk of dementia. Our systematic literature review and meta-analysis have focused on determining the association between fish consumption and risk of dementia worldwide. The previous meta-analysis papers[16-18] investigated the associations of both fish and omega-3 PUFA with combined mild and severe cognitive impairment (e.g. Mild Cognitive Impairment (MCI), Parkinson disease (PD), all-type dementia and Alzheimer's disease), not specifying exposure or outcomes, and failed to include some relevant studies [9]. In comparison with those previous reviews and meta-analyses[16-18], our systematic review and meta-analysis have elaborated specifically on the impact that the consumption of fish has on dementia and AD development. Our findings were based on the literature search without any limited selection and identified all eligible studies further including a new study from China (LMIC), which compensated for the scarce data from the LMIC countries. Adding in the new community-based cross-sectional study from China made our meta-analysis findings more robust and generalisable.

Our study has several potential limitations. Firstly, the 6-province health survey data was cross-sectional, and its causal-relationship between fish consumption and dementia risk could not be assessed. However, the findings of the study were similar to those in the cohort studies[9, 12, 13, 29, 37-39]. Secondly, similar to the majority of previous studies, in the 6-province survey we did not have information on different types (lean, fatty-fish, fried fish and seafood) and amount of fish consumed, which may hinder our inferences on specific types of fish and dementia. But overall, total fish consumption was significantly and inversely associated with dementia risk. We need further studies on specific types of fish consumption in relation to reduced dementia risk to warrant making more informative recommendations to the public. Thirdly, the identified studies used different levels of fish consumption for data analysis, making it difficult to assess the presence of a dose-response relationship between fish consumption and dementia risk. Using the RR data from the highest level group of fish consumption in some studies may be over-estimating the overall effect of fish consumption on dementia risk. However, when stratifying the articles for meta-analysis according to the number of the groups of their fish consumption level, we did not find that there was a trend of reduced risk of dementia or AD with increased number of the fish consumption level groups (Table 2, and online Table 4). If we included all RRs from different levels of fish consumption to pool the data (online Figure 2), the finding of the overall impact was not substantially changed (OR (95% CI): 0.80 (0.75-0.87).

In this systematic literature review we have noted that these 11 identified articles plus the 6-province study had various study designs, different locations, and various types of food frequency questionnaires to measure their fish intake. As the studies included in this meta-analysis were observational, the outcome of the current study was examined using the review guidelines of Bradford Hill[43] to provide evidence of a direct and causal relationship between fish consumption and risk of dementia and/or AD.

How strong are the associations?

The majority of the identified studies showed a moderate to high association of fish consumption with reduced risk of dementia[9, 12, 13, 29, 33, 36-39] after adjusting for possible confounders. Only one showed a weak or no association between fish consumption and the risk of dementia[29]. Our pooled data analysis showed a 20% to 30% increase in the risk of dementia and AD in people who did not eat fish in comparison with those who did. The magnitude of the association between fish consumption and the risk of dementia is similar to the impacts of environmental tobacco smoke (ETS) on the incidence of coronary heart disease (25% increased risk[44], and on lung cancer (27% increased risk[45]), and both have been taken as having a causal relationship with ETS exposure.

How consistent are the reported studies?

Of the 17 studied populations in this paper, 15 reported a reduction in the risk of dementia after a moderate to high intake of fish and adjusting for possible confounders[9, 12, 13, 34, 35, 37-39]. Two of the studies also showed a significant inverse association of fish consumption with the risk of mild to severe dementia and AD development, when the plasma phospholipid and the serum level of the AD participants were assessed for their DHA and EPA level[34, 35]. A significant reduction was also observed in the 6-province study from China. A consistent inverse association between fish consumption and dementia risk was observed in all seven countries that took part in the 10/66 dementia research group study, except India [33]. Our meta-analysis for these reviewed studies showed a high level of homogeneity, suggesting their consistent data.

Moreover, there are similar findings of the impact of fish consumption on cognitive function in children. Cohen et al[46] analysed the data of a randomized control trial (RCT) and demonstrated a 0.13-points increase in the Intelligence Quotient (IQ) of children when mothers received a DHA supplement of 100mg/day. A review by Eilander et al[7] established enhanced cognitive development in infants and children after maternal supplementation with omega-3 long-chain polyunsaturated fatty acids (LCPUFA) during pregnancy and lactation though they had inadequate evidence for an association with children over 2 years old. Ryan et al[47] also indicated in their review that neurocognitive development during childhood is enhanced when pregnant and lactating mothers are supplemented with DHA. These would support our findings of the impact of fish consumption on reduced risk of dementia.

How specific are the proposed fish consumptions and the response to outcome?

Of these identified articles , a few studies[12, 37, 38] investigated the fish intake based on fatty, lean, fried fish and seafood. The varying consumption of these types of fish might have affected the outcome of these studies. Huang et al[38] revealed a 28% reduction in the risk of developing dementia after the intake of fatty fish, while the consumption of lean fried fish produced no significant beneficial effect. The two major fish constituents (DHA and EPA omega-3 fatty acids) were associated with a reduced risk of developing dementia and cognitive decline[17, 48]. The dose-response impact of fish consumption on specific dementia, i.e. AD seemed to be stronger.

Is there a temporal relationship between exposure and response?

The observed association between fish consumption and dementia was prominent in all the prospective cohort studies[9, 12, 13, 29, 37-39], demonstrating a temporal association which signified that an exposure preceded the outcome. In the United State, Huang et al[38] followed up 2233 participants for 5.4 years and identified 378 new cases of dementia; the RR in participants with fish consumption was 0.79 (0.53-1.20). The Rotterdam study followed up 5395 participants for 9.6 years and observed 465 dementia cases developed, showing a RR of 0.95 (0.76-1.19) of dementia in relation to fish consumption[29]. The pooled data of RR between short and long-term follow up studies were similar (Table 2, seen in Results section).

Is there an exposure-response relationship?

An exposure-response relationship has been identified between different levels of fish consumption and risks of dementia and AD in our meta-analysis. The majority of identified studies [9, 12, 13, 29, 33, 36-39] showed this, with non-statistical significance. Morris et al[13] demonstrated a non-significant dose-response relationship of AD with fish consumption; RR 0.6

(0.3-1.3) in participants who consumed fish 1-3 times per month, 0.4 (0.2-0.9) in those who consumed fish once a week and 0.4 (0.2-0.9) in ≥ twice per week (trend p=0.07). However, other cohort studies[12, 37, 39] showed that in the highest level of fish consumption the reduced risk of dementia was not significant. This may be due to the small number of patients in these groups. Nevertheless, the pooled data in our paper (Table 3) across all the different levels of fish intake from the included studies have shown a significant reduction in the risk of dementia (Online Figure 2) and AD.

Is the association biologically plausible?

The biological mechanism exhibited by fish consumption in relation to the prevention of dementia may be as a result of the presence of omega-3 fatty acid as part of their constituents. The omega-3 fatty acid is a major component of neuronal membranes, with cardio-protective, anti-inflammatory, antioxidant and anti-atherogenic properties[40, 49, 50]. They have the capability to display a beneficial effect on the risk of developing dementia and AD, particularly vascular dementia[15, 28, 37]. Fish is a beneficial source of essential amino acids, micronutrients and vitamins, thus increasing the protective effect they exhibit on the risk of developing all cause dementia and cognitive impairment[51]. Fatty fish are known to be richer sources of DHA and EPA, which are naturally found in trout, tuna, salmon, sardines, herring[52], and mackerel, but minimal sources are found in lean fishes, such as cod, haddock, and halibut. An increase in the intake of fatty fish may also be positively associated with a decrease in the level of the consumption of saturated fat, thus reducing the risk of stroke[3]. This might be as a result of the anti-inflammatory, antithrombotic, antioxidant and anti-amyloid properties of its omega-3 fatty acids component[41, 49, 50].

Is the evidence coherent with knowledge of the natural history of disease?

Dietary fatty acid has displayed a significant effect on the risk of developing cardiovascular disease,[41, 53, 54] depression[55] and children's cognitive impairment[7, 56]. This association involves the higher consumption of saturated fat and cholesterol and lower consumption of polyunsaturated fatty acid (omega-3 fatty acid). Omega-3 fatty acid intake has been associated with reduced risk of cognitive impairment and dementia through several possible mechanisms. They display a cardio-protective property that makes them protective over several cardiovascular risk factors such as stroke, atherosclerosis, and inflammation through influence on brain development and proper membrane function[28, 57]. They have exhibited their cognitive-enhancing effect during infancy, childhood, old age and among adults with neurocognitive impairments in some clinical trials[57, 58]. This beneficial effect was supported by the outcome of the Chicago Health and Aging six year prospective cohort study (CHAP) that involved fish intake and cognitive impairment[10], and in the result revealed in the Zutphen Elderly five year prospective cohort study of fish consumption, omega-3 fatty acid and cognitive decline[11]. The China Health and Nutrition Survey also maintained that adequate intake of fish does lower cognitive decline [59].

Is there experimental evidence?

Numerous animal studies have demonstrated the positive role that omega-3 fatty acids (a fish constituent) play on brain development. They increase neurotransmission[60], enhance memory capabilities[61], enhance the excitability regulation of the neuronal membrane[62], decrease the neurons ischemic damage[63] and increase the cerebral flow of blood[64]. Experimental studies of rats that had a reduced level of DHA in their diet exhibited an impaired cognitive function, while those animals that had a prolonged administration of DHA demonstrated an enhanced gain in memory[65]. These studies confirmed that the exposure of animal models to the intake of DHA positively influenced their neurological status.

Does the evidence accord by analogy with that from other fields?

Previous studies showed a significant beneficial effect of intake of omega-3 fatty acid as a supplement on dementia and cognitive impairment[10, 11]. Findings from a randomized control trial (RCT) that involved supplementing the treatment group with arachidonic acid (ARA) and DHA, part of omega-3 fatty acids components, did exhibit a significant beneficial effect on the cognitive function in the treatment MCI group, while the placebo group showed no significant beneficial effect[66]. A similar beneficial effect was observed among an MCI group in a RCT of 46 participants of (23 mild or moderate AD and 23 MCI) that were randomized to receive either an omega-3 PUFA acids treatment or an olive-oil (placebo)[67]. In a one-year RCT that investigated the effects of fish oil supplementation on cognitive function in older adults, Lee et al[68] found a significant beneficial effect within a short-term and after a 12 months period on participants working memory, immediate verbal memory and in the delayed recall ability among the treatment group that were supplemented with fish oil. The results of the current study are thus consistent with the findings of these studies, thereby acknowledging the positive influence that fish and its constituents have on cognitive function.

Implication of the study findings

Our study demonstrates a significant beneficial effect of eating fish on reducing dementia. The epidemic of dementia has become a public health problem worldwide. As the world population, has been ageing, the number of people with dementia will continue to rise. The vast majority of the increment is expected to be in LMICs, which currently hold 58% of people living with dementia, with further increment by the year 2050[1]. In China, there is a growing number of people living with dementia due to the population of older people with mixed characteristics (e.g. low level of education but rapidly increased income)[69]. Our study demonstrated a significant association of higher fish consumption with reduced risk of dementia, which further indicates the potential importance of consuming fish in preventing from dementia worldwide. At present, the global per capita fish consumption level is estimated to be an average of 20 kg per year[70], and is lower in LMICs (18.8 kg) than those in high-income countries (26.8kg). Our study demonstrated consistent findings of the impact of fish consumption on the risk of dementia between LMICs and high-income countries. People should thus increase their level of fish consumption, especially in areas where the consumption is quite low such as LMICs, to reduce the burden of dementia. Also, people living in high income countries, including the UK should be informed of the beneficial impact of fish consumption to increase its intake further.

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Table 1: Numbers, percentages and odds ratios (95% confidence intervals) of people with dementia in different levels of fish consumption: the six-province study in China

Frequency of fish consumed over the past 2 years	Dementia					Multivariate-adjusted analysis			
	No		Yes						
	n	(%)	n	(%)	*P**	OR†	95%CI		*P*
Fish									
No	1438	94.1	90	5.9	<0.001	Ref.			
Once a week	2516	95.6	115	4.4		0.79	0.49	1.29	0.355
More than twice a week	1875	96.7	63	3.3		0.59	0.38	0.90	0.014
>=once a day	826	93.4	58	6.6		0.76	0.55	1.04	0.089
Total	*6655*	*95.3*	*326*	*4.7*					

*Chi-square test P value. †Adjusted for age, sex, province, urban-rural areas, education level, smoking status and stroke.

Table 2: The pooled analysis results for dementia risk in people with fish consumption versus those with no or lower levels of fish consumption, by country of study and by study data analysis

Variable for subgroup data analysis	Nos of studies	Nos of studied populations	Nos of Participants	Nos of dementia	RR (95% CI)
By study design					
Cross-sectional studies[33]*	2	8	21,937	1671	0.79 (0.72-0.88)
Prospective cohort studies (follow up ≤ 5 years) [9, 37]	2	2	8,327	323	0.67 (0.38-1.18)
Prospective cohort studies (follow up >5 years) (12, 29, 38, 39)	4	4	9,532	1,112	0.85 (0.72-1.00)
By level of fish consumption §					
Continuous [9, 12, 29, 33, 36-39] *	9	15	39,853	3,139	0.80 (0.74-0.87)
Only 2 levels[39]	1	1	488	99	0.61(0.28-1.33)
Only 3 levels[9, 12, 29, 36]	4	4	7,110	710	0.86 (0.71-1.03)
4 levels[37, 38] *	3	3	17,299	985	0.77 (0.61-0.98)
By country of study in terms of income					
High income countries [9, 12, 29, 36-39]	7	7	17,916	1,468	0.83(0.71- 0.97)
Low and middle income [33] and the six-province study of China	2	8	21,937	1,671	0.79 (0.72 -0.88)

Abbreviations: CI: Confidence Interval; RR: Relative Risk.

*including the new community-based cross-sectional study of the six-province health survey in China

§ fish consumption level: "Continuous" means that the authors analysed data of fish consumption for the results presentation; "Only 2 levels" means that the authors analysed the data of fish consumption in two levels, based on the questionnaire record or grouping them into two; "Only 3 levels" means that the authors analysed the data of fish consumption in three levels; and "4 levels" means that the authors analysed the data of fish consumption in 4 levels.

Table 3: Dose-response relationship between fish consumption and risk of dementia and AD †

Consumption of Fish	Dementia				AD			
	Nos of Studies *	Nos of Participants	Nos of dementia	RR (95% CI)	Nos of Studies	Nos of Participants	Nos of AD	RR (95% CI)
Low level	6[29, 36-39] §	23,239	1582	0.84 (0.72-0.98)	6[13, 29, 37-39, 71]	18,432	1,075	0.88 (0.74-1.04)
Middle level	7[9, 12, 29, 36-38] §	24,409	1695	0.78 (0.68-0.90)	5[9, 13, 29, 37, 38]	16,770	899	0.79 (0.65-0.96)
High level	3[37, 38] §	17,299	985	0.77 (0.61-0.98)	3[13, 37, 38]	11,133	504	0.67 (0.58-0.78)

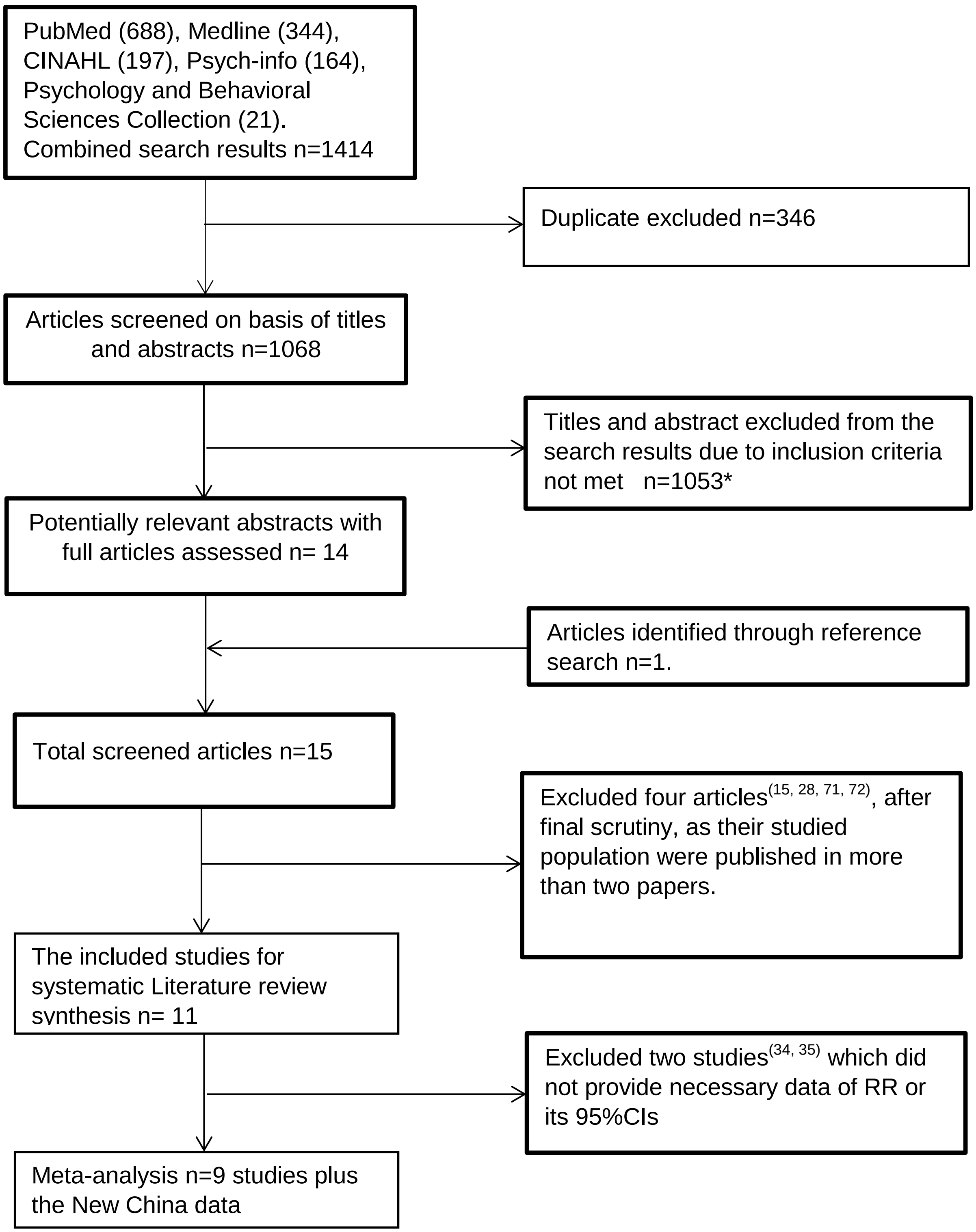
Abbreviations: CI: Confidence Interval; RR: Relative Risk.

† each of these low, middle and high levels of fish consumption versus no or lowest consumption of fish.

*The same number of studied populations

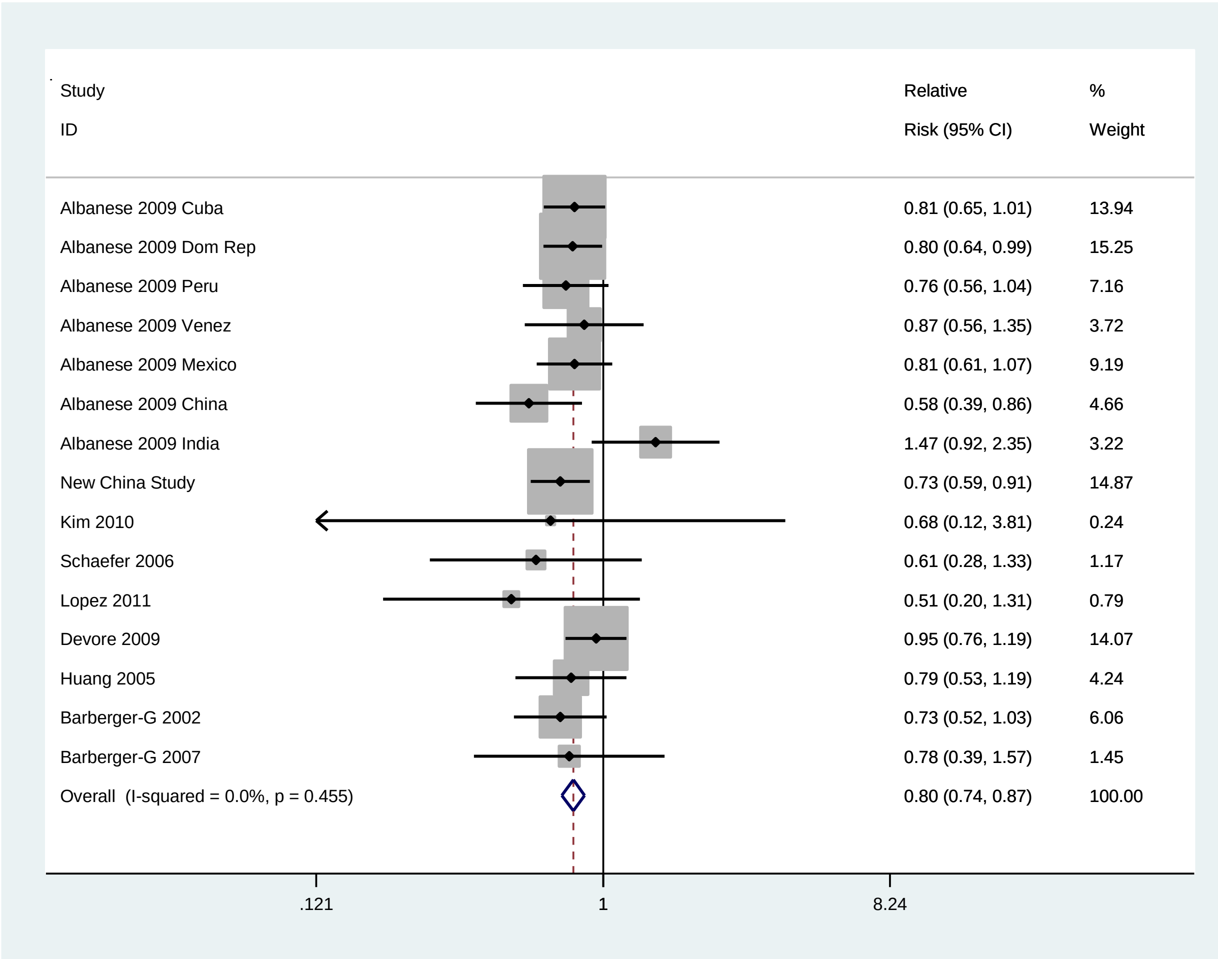
§including the new community-based cross-sectional study of the six-province health survey in China

Figure 1. Diagrammatic expression of the literature search technique



*Reasons for exclusions: Appropriate outcome not reported, Randomized control trial; Assessed another exposure other than fish, Assessed another outcome other than dementia or AD, Articles on importance of fish to dementia and brain development, News briefs, Articles on elderly nutrition, Literature review/meta-analysis, Presentation

Figure 2. Forest plot showing the association of fish consumption and dementia risk



* One of the 9 studies used for the meta-analysis (Morris et al[13]) provided the RR result for Alzheimer's Disease only, and therefore it was not included in the above analysis.